**Review Paper**
**Examen critique**

# How do the atypical antipsychotics work?

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Understanding the action of atypical antipsychotics is useful in exploring the pathophysiology of schizophrenia and in synthesizing drugs that improve various domains of psychopathology without unwanted side effects. In animal models, atypical antipsychotic drugs appear to have a preferential action in the limbic dopaminergic system. Regionally specific action has been studied by measuring the amount of Fos protein produced in a particular brain region as a consequence of a drug's effects on the c-*fos* gene. Evidence suggests that the atypical and typical antipsychotic drug-induced increases in Fos levels in the nucleus accumbens are related to improvements in positive symptoms, whereas Fos increases in the prefrontal cortex, with the atypical antipsychotics only, correlate with negative symptom improvement. The extrapyramidal effects seen with typical antipsychotics are thought to be related to Fos increases in the striatonigral pathway. However, studies of Fos levels in specific brain regions reveal only the site of action, not the mode of action. The finding that atypicality is related to surmountable $D_2$ dopamine receptor blocking provides another venue to define and explore atypical antipsychotic drug action.

Il est utile de comprendre l'action des neuroleptiques atypiques dans l'étude de la pathophysiologie de la schizophrénie et la synthèse de médicaments qui améliorent divers domaines de la psychopathologie sans produire d'effets secondaires indésirables. Dans des modèles animaux, les neuroleptiques atypiques semblent avoir un effet préférentiel dans le système dopaminergique limbique. On a étudié des actions spécifiques régionales en mesurant la quantité de protéine Fos produite dans une région particulière du cerveau à la suite des effets d'un médicament sur le gène c-*fos*. Tout semble indiquer que les augmentations des taux de Fos produites par les neuroleptiques atypiques et typiques dans le noyau accumbens sont reliées à des améliorations de symptômes positifs, tandis que les augmentations des taux de Fos dans le cortex préfrontal provoquées par des neuroleptiques atypiques seulement présentent un lien avec l'amélioration de symptômes négatifs. On pense que les effets extrapyramidaux causés par les neuroleptiques typiques sont reliés aux augmentations des taux de Fos dans la voie striatonigrale. Des études des taux de Fos dans certaines régions précises du cerveau ne révèlent toutefois que le type de l'action et non son mode. La constatation indiquant que le caractère atypique est relié à un blocage surmontable des récepteurs de la dopamine $D_2$ offre un autre moyen de définir et d'explorer l'action des neuroleptiques atypiques.

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## Introduction

A growing number of atypical antipsychotic drugs have emerged over the last few years. Although these new drugs are lumped together as "atypical," their widely varying chemical structure and pharmacological actions indicate their heterogeneity. Understanding the mode of action of the atypical antipsychotic drugs is useful in exploring the pathophysiology of schizophrenia and establishing realistic goals for treating schizophrenia.

## Animal models of antipsychotic action

Generally, pharmacologic tests employed in animals for predicting the antipsychotic effects of drugs in humans are based on 2 principles.

- The ability of the drug to block the action of dopamine (DA) in animals: 2 standard tests are used to assess this. When a $D_2$ receptor antagonist is injected into a rat, it will remain immobile for an extended period of time when placed in an unnatural position. This immobility, called catalepsy, is caused by the blockade of DA receptors within the neostriatum and is considered to be a predictor of extrapyramidal symptom (EPS) inducing potential in humans. The second test, the blockade of a conditioned avoidance reaction, is extensively employed as a predictor of antipsychotic action. After an animal has learned to respond to a sensory cue and move away from a floor to avoid electric shock, antipsychotic agents will block its ability to respond to the sensory cue presented before the shock.[1]
- The ability to counteract the effects of dopaminergic drugs: the administration of *d*-amphetamine, a dopaminergic agent, produces locomotor stimulation and stereotypy in rats. Neuroleptic agents, as well as atypical antipsychotic drugs,[2,3] decrease amphetamine-induced hyperactivity.

All antipsychotic drugs are screened in animals on these tests.

Until recently, it was thought that both cataleptic potential and blocking of a conditioned avoidance reaction in animals was necessary for predicting antipsychotic action in humans. The finding that atypical antipsychotic agents such as clozapine, remoxipride, thioridazine and olanzapine block conditioned avoidance in much smaller doses than those required to produce catalepsy[3–5] helped to clarify the meaning of the animal pharmacologic tests. Clinically, these drugs have been proven to be effective for treating psychosis, and they produce fewer EPS in patients than neuroleptic agents (i.e, typical antipsychotics). In nonhuman primates, the effective antipsychotic agents such as clozapine and sertindole do not produce dystonia.[6] Thus, catalepsy in animal pharmacologic tests predicts EPS, and blockade of conditioned avoidance predicts antipsychotic potential in humans.

The observation that injections of both typical and atypical antipsychotic agents into the nucleus accumbens (NAC) antagonizes amphetamine-induced locomotor activity suggests that this nucleus may be the site of antipsychotic action. Metoclopramide, a benzamide derivative, even in doses that produce catalepsy, cannot block this effect.[7] This is not a potent antipsychotic drug, but it can induce EPS. Generally, atypical antipsychotic drugs can be distinguished by a greater degree of separation of dose–response curves for antipsychotic efficacy and EPS liability than typical antipsychotic drugs.[8–10]

Recently, other animal pharmacologic tests such as prepulse inhibition and paw tests have been introduced.[11] Hopefully, in future, animal models will help to predict not only antipsychotic action and EPS potential but also effectiveness on cognitive, negative and mood measures. The neuroleptic agents and the atypical antipsychotic drugs may lie on the same continuum for EPS liability, but animal models indicate that parkinsonian symptoms are not necessary for antipsychotic action and have provided a framework for developing antipsychotic drugs with no EPS.

## Antipsychotic action on specific brain sites

Proto-oncogenes, each of which serves a specific function, are normal cellular genes that cause cellular transformation. They are also called immediate early genes (IEGs) because in response to neurotransmitters and drugs, their transcription is transiently activated in neurons within minutes without new protein synthesis. These cellular IEGs include members of the related *fos* and *jun* families and *zif/268*. The *fos* family of genes has a prefix c in animals and v in viruses. The protein produced, Fos, is present in very small quantities in many neuronal cells under resting conditions. In response to a stimulus, c-*fos* mRNA is produced and translocated into the cytoplasm where it is translated into Fos protein. Fos protein is then translocated back

to the nucleus where, in conjunction with a member of the Jun family, it binds to the activator protein-1 (AP-1) site on the promoter regions of the numerous target genes and regulates their expression. Diverse external stimuli can activate the IEGs by stimulating the production of a calmodulin-dependent protein kinase.

The proto-oncogene c-*fos* is a useful marker to map changes in neuronal activity.[12,13] The ability of various neurotransmitters to increase c-*fos* expression in the central nervous system suggests that c-*fos* induction can occur as a consequence of synaptic activation. Fos binding to DNA changes the response of an organism for as long as a drug is given, but does not permanently change the gene. This phenomenon is called a phenocopy, in contrast to phenotype.

Neuroleptics and atypical antipsychotic drugs induce c-*fos* in various areas of the brain.[14–16] This differential distribution is useful in identifying the brain regions that are targets for these drugs. Antipsychotic drugs have been reported to increase c-*fos* expression in the striatum, NAC, medial prefrontal cortex (PFC) and lateral septal nucleus. Recently, attention has focused on the thalamic region as well.

### *Striatum*

The striatum is divided into the dorsolateral region, which includes caudate and putamen, and the ventromedial region, which interacts with sensorimotor and limbic association cortices. Haloperidol[14] and raclopride[17] induce Fos in the striatum. This effect is considered to be due to a blocking of DA receptors on striopallidal neurons.[15,18,19] A number of additional findings support the possibility that Fos production is the direct result of $D_2$ blockade; in particular:

- coadministration of a $D_2$ receptor agonist prevents the induction of c-*fos* by haloperidol in the striatum;[15]
- dopaminergic agents such as cocaine and *d*-amphetamine decrease neuroleptic-induced striatal c-*fos* expression;[18,20]
- a close topographical relationship exists between neuronal Fos protein and $D_2$ receptor distribution;
- 6-hydroxydopamine (6-OHDA) lesions of the mesencephalic DA system block haloperidol-induced c-*fos* expression in the striatum and haloperidol- and clozapine-induced c-*fos* expression in the NAC.[17]

These results suggest that haloperidol increases the number of *fos*-positive neurons in the striatum by means of its $D_2$ receptor blocking ability.

Although evidence suggests that increased Fos production in dorsal striatum correlates with EPS, a recent study[21] indicates that these findings may be applicable to short-term treatment only; Fos in the striatum was found to be downregulated by long-term treatment with clozapine and haloperidol. Haloperidol, but not clozapine, led to markedly enhanced Fos-B-like protein levels in the caudate putamen in rats. Thus, acute EPS may be related to Fos in the striatum, but long-term EPS may be related to Fos-B in caudate putamen. Whether tardive dyskinesia, a long-term EPS, is related to changes in caudate putamen is unknown.

An increase in striatal c-*fos* expression associated with the administration of antipsychotic agents in animals is predictive of EPS in humans, and low or no c-*fos* production in the striatum may be related to a low potential for producing EPS.[22] The antimuscarinic agent, scopolamine, attenuates haloperidol-induced c-*fos* expression in the striatum. This suggests that the antimuscarinic action of clozapine may be responsible for its failure to induce c-*fos* in the striatum.[23] However, because many other atypical antipsychotic agents that lack antimuscarinic action also fail to induce c-*fos* in the striatum, the antimuscarinic action of clozapine must not be the sole cause.

### Enkephalin in the striatum

Enkephalin may be involved in regulating c-*fos* in the striatum and thereby affecting EPS. Haloperidol administration increases enkephalin mRNA in the striatal neurons,[24] whereas clozapine causes a small increase. Moreover, after antipsychotic drug administration, c-*fos* expression and enkephalin increases occur in the same cells,[14] suggesting that c-*fos* may be located in enkephalinergic neurons and that enkephalin may be a target for *fos* expression.

### *Nucleus accumbens*

The NAC has 2 divisions: the shell and the core. The shell is allied with limbic circuits and the core, with the extrapyramidal system. All neuroleptic drugs increase c-*fos* in both the shell and the core of this nucleus.[14,15] Atypical antipsychotic drugs, however, increase c-*fos* in the shell but not in the core. Wan et al[25] compared the effects of the intraperitoneal administration of haloperidol, chlorpromazine, thioridazine, clozapine, raclopride, risperidone and ritanserin on Fos expres-

sion in the rat brain. Ritanserin did not increase Fos in any region, indicating 5-$HT_2$ serotonin receptor antagonism alone is not responsible for the observed effects of antipsychotic drugs. The single shared effect of all the antipsychotic preparations was the increased Fos-like immunoreactivity in the NAC. Metoclopramide, a drug that produces EPS without antipsychotic effects, induces Fos in the core but not in the shell, suggesting that Fos expression in the shell of the NAC may be related to clinical improvement of positive symptoms of schizophrenia.

All antipsychotic agents that have been tested act on the shell of the NAC and improve positive symptoms, but only the atypical antipsychotic agents act on negative symptoms. Accordingly, c-*fos* expression in the shell of the NAC is probably not associated with improvement of negative symptoms.

**Neurotensin**

Perikaryal neurotensin immunoreactivity is largely absent in the rat striatum except after striatal DA depletion or $D_2$ receptor blockade. After $D_2$ receptor blockade, neurotensin immunoreactivity occurs in 2 subpopulations of striatal neurons.[26] One subpopulation, located mainly in the rostral, dorsomedial and ventromedial aspects of striatum, comprises moderate-to-large sized cells. These exhibit intense neurotensin immunoreactivity but rarely display Fos immunoreactivity.[27,28] A second subpopulation, predominantly in the patch and matrix compartments in the lower quadrant of the striatum, is prominent after reserpine administration and shows very light neurotensin immunoreactivity.[28]

Haloperidol, chlorpromazine, pimozide and trifluoperazine[29] induce Fos that is frequently colocalized with neurotensin in the dorsolateral striatum[30] and the NAC.[31,32] In contrast, clozapine has been found to increase neurotensin concentrations in the NAC only.[33–35] With long-term treatment, haloperidol, but not clozapine, increases neurotensin in the globus pallidus.[36] With sertindole, the effect in the NAC is dose dependent, and at higher doses, selectivity is lost.[37] Intraventricular injections of neurotensin antagonize apomorphine-induced locomotor activity but not stereotypy in rats[38] and selectively increase the number of spontaneously active neurons in $A_{10}$ but not $A_9$ areas,[39] both of which are indicative of its antipsychotic activity without significant EPS.

Neuronal Fos-like immunoreactivity and neurotensin/neuromedin N mRNA are expressed in the same population of striatal neurons after a single injection of haloperidol.[40] This finding represents an essential anatomical link between c-*fos* and neurotensin. Fos-like immunoreactivity was seen in neurons within 2 hours, and increases in neurotensin were noted 7 hours after a haloperidol injection.[14,41] This suggests that Fos may be necessary for the induction of the neuromedin gene. Injection of an antisense oligonucleotide to c-*fos* blocks the haloperidol-induced increase in Fos and subsequent mRNA for neurotensin.[30] Thus, Fos appears to be a second messenger in the induction of endogenous neuropeptides. The practical therapeutic use of neurotensin in psychosis should therefore be explored.

*Medial prefrontal cortex*

The prelimbic, dorsal and anterior cingulate, and medial precentral cortices collectively make up the PFC.[42] These areas receive afferents from $A_{10}$ DA neurons in the ventral tegmentum of the midbrain.[43] The infralimbic region also receives the same afferents as well those from the thalamic paraventricular nucleus.[44] Stimulation of the dorsomedial thalamic nucleus increases the firing rate of PFC pyramidal cells.[45,46] These medial thalamic projections to the frontal cortex are glutamatergic.[46,47]

Unlike haloperidol, clozapine increases Fos-positive neurons in the PFC. The Fos is selectively restricted to the pyramidal cells in the deeper layers of the ventral aspects of the rat PFC, including infralimbic and prelimbic cortex, but not the medial central cortex. Other atypical antipsychotic drugs (but not neuroleptics and remoxipride) also increase Fos in the PFC.[48] Guo et al[49] used brain lesion, pharmacologic and immunohistochemical techniques to explore the receptor mechanisms by which clozapine increases c-*fos* expression in the PFC. Reduction of the serotonin, norepinephrine or DA content by selective lesions in the brain did not decrease clozapine-induced c-*fos* expression in the rat PFC, suggesting it is unlikely that these mechanisms are involved in the clozapine-induced changes in c-*fos* expression in the PFC.[17,49] An alternate explanation for this action has been put forward — that c-*fos* expression in the PFC is the drug-induced downstream effect of GABA afferents from the paraventricular nucleus of the thalamus to the PFC. Clozapine may exert its action on the PFC indirectly through afferent input from the medial thalamus, hippocampus, entorhinal cortex and basolateral amygdala.

The most likely site of action of atypical antipsychotic drugs on negative symptoms of schizophrenia is the PFC.[17] This is based on the fact that atypical antipsychotic drugs that improve negative symptoms increase c-*fos* expression in the PFC in animal pharmacologic tests. However, the effectiveness of atypical drugs on primary negative symptoms has not been conclusively proven. A number of interpretations are possible in this regard — that c-*fos* expression in the PFC is:

- coincidental only, and it is the absence of EPS with atypical drug administration that is responsible for the apparent improvement of negative symptoms;
- an indirect effect of drug action elsewhere;
- directly correlated with improvement of negative symptoms. This assumption is supported by the findings that medial sulcal atrophy in the PFC decreases the effectiveness of clozapine on negative symptoms. Neuropsychologic testing and neuroimaging findings also point to a frontal lobe defect.[50,51] Patients with schizophrenia have a defect in smooth eye tracking which is associated with the medial PFC. Because clozapine acts on the PFC and not on the medial PFC, it does not alleviate the defect in smooth eye tracking.

*Lateral septal nucleus*

Clozapine greatly increases the number of Fos immunoreactive neurons in the lateral septal nucleus as well.[52] Haloperidol and not raclopride produced a modest increase in c-*fos* expression in the lateral septal nucleus, indicating that *fos* production may not be related to $D_2$ receptor blockade. Apart from risperidone, all of the antipsychotic drugs tested to date elevate Fos-like immunoreactivity in the lateral septal nucleus, suggesting that this limbic structure is important for antipsychotic activity.[52] In contrast to the PFC, the lateral septum contains abundant 5-$HT_{1A}$ receptors and very few 5-$HT_2$ receptors.[53] Neither clozapine nor haloperidol appear to block 5-$HT_{1A}$. Therefore, the increase of Fos in the septal area may be due to mechanisms unrelated to 5-HT and DA.

*Thalamic paraventricular nucleus*

The paraventricular nucleus of the thalamus is in a pivotal location between the reticular formation and forebrain DA system and may serve an important role in the pathophysiology of schizophrenia. Clozapine administration increases Fos in the thalamic paraventricular nucleus, which provides glutamatergic projections to the PFC and the NAC; these projections may be associated with the observed c-*fos* induction in the PFC.[17,54] Comparable doses of raclopride, sulpiride, remoxapride and haloperidol did not induce Fos in this region, whereas loxapine and very high doses of haloperidol induced a modest increase. Also, a $D_1$ antagonist did not induce Fos or alter clozapine-induced Fos.[54] There is electrophysiological evidence that iontophoretically applied clozapine, but not haloperidol, can reduce the inhibitory actions of a 5-HT receptor agonist on pyramidal cells in the PFC.[55]

## General pattern of c-*fos* distribution

Haloperidol administration induces c-*fos* expression in the NAC, lateral septal nucleus and striatum, and clozapine increases c-*fos*-positive neurons in the all the above-mentioned areas as well as the medial PFC.[16,17,56,57] This suggests that the typical and atypical antipsychotic drugs evoke different patterns of neuronal activity and that the different clinical profiles of drugs may be related to the regionally different effects. $D_2$ receptor antagonism is not sufficient to explain the unique pattern produced by clozapine because it is common for both drug groups.[58] The exact receptor mechanisms underlying antipsychotic drug-induced c-*fos* expression in the medial PFC and other regions remain unknown.

*DA receptors*

Although the relation between $D_2$ receptor blocking and antipsychotic potential is well established, the relation is not linear. In vitro studies provide some support for the finding that blocking over 80% of the receptors produces EPS and thus affects relative antipsychotic efficiency.[59] Conversely, $D_2$ receptor occupancy of less than 80% produces atypical features, including low EPS.[60] In a single-photon emission tomography (SPET) study employing a $D_2$ receptor ligand in EPS-free patients,[61] olanzapine displayed a level of binding in the brain between that of haloperidol and clozapine. In striatal $D_2$ receptor binding, olanzapine was similar to clozapine.[61] These results argue that moderate $D_2$ receptor antagonism is associated with fewer EPS. The looseness of attachment of an antipsychotic drug to the $D_2$ receptor seems to differentiate typical and atypical drugs.[62–64] Typical drugs are firmly attached and atypi-

cal drugs are loosely attached to $D_2$ receptors, and thus, the latter do not induce EPS.

The actions of antipsychotic drugs on $D_1$, $D_3$ and $D_4$ receptors have also been explored. $D_3$ receptors are expressed mainly in the olfactory tubercle, NAC, island of Calleja and hypothalamus.[65–67] $D_4$[68] receptors have a unique distribution, with the highest levels in the PFC, and $D_3$ receptors are distributed in the NAC, major island of Calleja and lateral septal nucleus. Quinpirole, which has approximately equal antagonist affinities for $D_3$ and $D_4$ receptors, induced a significant decrease in clozapine-induced c-*fos* expression in PFC, NAC, major island of Calleja and lateral septal nucleus. In contrast, the more selective $D_3$ receptor agonist 7-OH-DPAT[69,70] significantly reduced clozapine-induced increases in c-*fos* expression (Fos protein levels) in the major island of Calleja, NAC and lateral septal nucleus, with no effect on the Fos level in the PFC. These data suggest that the action on $D_3$ receptors may mediate the c-*fos* effects in the NAC, major island of Calleja and lateral septal nucleus, whereas $D_4$ receptors may be responsible for the action in PFC.

Based on the selective antagonism of clozapine at $D_4$ compared with $D_2$ receptors, expectations that $D_4$ receptor blockers would improve schizophrenia ran high.[71] Roth et al[72] assessed the affinities of 13 atypical and 12 typical antipsychotic drugs on $D_4$ receptors and examined $D_4/D_2$ ratios. Many atypical drugs (e.g., melperone, quetiapine, fluperlapine) had very little $D_4$ receptor blocking activity, and many typical (e.g., loxapine, chlorpromazine, fluphenazine, mesoridazine, thioridazine, trifluoperazine) and some atypical drugs (i.e., olanzapine, clozapine, risperidone, zotepine, tiospirone) drugs had high $D_4$ affinities. Interestingly, the ratios of $D_2/D_4$ did not differentiate the typical and atypical agents but 5-$HT_{2A}/D_2$ ratios did. Moreover, a selective $D_4$ receptor antagonist, L-745,870, was found to be ineffective in the treatment of schizophrenia in a placebo-controlled study.[73]

The role of $D_1$ receptors in the pathophysiology of schizophrenia is also unclear. Repeated administration of cocaine and amphetamine produces long-term behavioural changes as well as addiction. Cocaine enhances extracellular DA by blocking reuptake, and amphetamine does the same by increasing DA release. The effects of psychomotor stimulants occur in striatal neurons that selectively express the $D_1$ receptor subtype.[74–77] Amphetamine or cocaine administration in the $D_1$-receptor-deficient mouse[77] does not induce Fos-like activity, and pure $D_1$ receptor antagonists have been reported to produce catalepsy in rats[78,79] and dystonia in monkeys primed with typical neuroleptics.[80] These findings suggest that $D_1$ receptors may have a role in producing EPS or that $D_2$ receptors may act through $D_1$ receptors to produce EPS.

*Serotonin receptors*

Atypical antipsychotics block serotonin 5-$HT_2$ receptors.[58,81–83] When the ratio of 5-$HT_2$ to $D_2$ receptor blocking is greater than 1, atypical antipsychotic action such as therapeutic effects on negative symptoms and few EPS are noted. Although 5-$HT_2$[84] receptor blockade and atypical profile correlate, the exact mechanisms by which 5-$HT_2$ blocking improves negative symptoms and induces fewer EPS are unclear. It will be recalled that positive symptoms are associated with a hyperdopaminergic state in the limbic lobe, which is rich in dopaminergic innervation. Serotonin inhibits DA release, and in the limbic lobe, with high 5-$HT_2$ and low $D_2$ receptor density, $D_2$ receptor blocking action prevails and positive symptoms are controlled. Negative symptoms, on the other hand, are associated with a hypodopaminergic state in the frontal lobe, which is rich in serotonergic innervation. Here, with the rich distribution of 5-$HT_2$ and sparse distribution of $D_2$ receptors,[85] serotonin inhibits DA release and the hypodopaminergic state of the frontal lobe becomes normal, thereby improving negative symptoms. Thus, the differential distribution of $D_2$ and 5-$HT_2$ receptors explains why atypical antipsychotic drugs exert opposite action on DA transmission in the frontal and limbic lobes.

Given that $\alpha_1$ adrenergic[86,87] and $\alpha_2$ adrenergic[88] receptor blockade has also been proposed to be involved in the mechanism of action of the new antipsychotics, "multireceptor" action may actually explain the unique clinical profile of atypical antipsychotic agents (Table 1). Clozapine, which acts on many different receptor types, has been proven to be the clinically most effective drug with the least EPS. Olanzapine also exhibits multireceptor action, whereas risperidone and sertindole have predominantly $D_2$ and 5-$HT_2$ receptor blocking effects. Any subtle differences in the action of the 2 groups of drugs remain to be elucidated.

## Electrophysiological activity

Individual DA cells show both tonic and phasic activity.

**Table 1: Action of atypical antipsychotic drugs at receptors**

| Atypical antipsychotic | Receptor, action | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Dopamine | | | Norepinephrine | | | | |
| | $D_1$ | $D_2$ | $D_4$ | $\alpha_1$ | $\alpha_2$ | Histamine 1 | Acetylcholine | Serotonin $5\text{-}HT_{2A}$ |
| Clozapine | + | + | + | + | + | + | + | + |
| Risperidone | + | + | + | + | + | + | 0 | + |
| Olanzapine | + | + | + | + | + | + | + | + |
| Sertindole | + | + | ? | + | + | + | + | + |
| Quetiapine | + | + | 0 | + | + | + | 0 | + |
| Ziprasidone | + | + | ? | + | 0 | + | 0 | + |

Note: + = drug blocks receptor, 0 = drug does not block receptor, ? = effects at receptor unknown.

Spikes that represent the firing of the single neuron form the background noise or tonic activity against which bursts of 5–20 spikes/s form the signals or phasic activity. When phencyclidine, which mimics schizophrenia, is injected into an animal, DA neurons in the ventral tegmental area show increased tonic activity and decreased phasic burst activity. This suggests that the positive symptoms of schizophrenia may be due to increased tonic activity, bringing a low signal-to-noise ratio. Atypical antipsychotic drugs act on dorsal and ventral tegmental areas differently; they downregulate the firing rates in the ventral but not the dorsal tegmental area, and this has 2 important effects: the hyperdopaminergic state in the limbic area is normalized, and the extrapyramidal system is not affected (i.e., no EPS). Typical antipsychotics increase the actively firing cells in both $A_9$ and $A_{10}$, whereas atypical antipsychotics affect the $A_{10}$ areas only.[89] Long-term administration of typical antipsychotic drugs decreases the firing of both $A_9$ and $A_{10}$ areas due to depolarization block. Atypical drugs quetiapine,[90] olanzapine,[4] sertindole[91] induce depolarization block in $A_{10}$ only, and thus, the antipsychotic effect is produced without EPS.[92,93]

## Conclusions

With knowledge of the intracellular and genetic action of antipsychotic drugs, the site of action of these drugs is better understood. Evidence suggests that $D_2$ receptors are related to improvement in positive symptoms, and such an action may reside in the shell region of the NAC. Similarly, data indicate that the medial PFC may mediate antipsychotic effects on negative symptoms. However, other possibilities should also be entertained; other regions may be involved as well, and these effects may be mediated by some not-yet-defined afferents. The brain regions associated with cognitive symptoms remain to be delineated.

Although c-*fos* genes provide some structural basis for the symptoms of schizophrenia, the action on the receptors are not clear. $D_2$, $D_3$ or $D_4$ receptors, or all of them in combination, may be involved in the alleviation of positive symptoms, and negative symptoms may be due to a hypodopaminergic state in the frontal lobe; 5-HT receptors may play a role in this regard. On the other hand, it is likely that the selective action of the new drugs on the ventral and not dorsal tegmental nucleus and the effect on the paraventricular nucleus of thalamus may also play a part in improving negative symptoms.

Robertson and colleagues[52] proposed a new definition of atypicality. They suggest that if the number of Fos-positive cells in the NAC is greater than the number of Fos-positive cells in the striatum, the drug should be considered atypical. This index allows atypicality to be quantified, but its usefulness requires further validation. In addition, the concept that the ability of the drug to bind to $D_2$ receptors in a reversible and surmountable fashion may also contribute to atypicality should be studied further.[94]

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